

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
3 June 2004 (03.06.2004)

PCT

(10) International Publication Number  
WO 2004/045604 A1

- (51) International Patent Classification<sup>7</sup>: A61K 31/352, 41/522, 35/00, A23L 1/29, A61P 3/04
- (74) Agents: VAN WESTENBRUGGE, Andries et al.; Nederlandsch Octroibureau, Scheveningseweg 82, P.O. Box 29720, NL-2502 LS The Hague (NL).
- (2) International Application Number: PCT/NL2003/000198
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 18 March 2003 (18.03.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 10/295,987 18 November 2002 (18.11.2002) US
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): N.V. NUTRICIA [NL/NL]; P.O. Box 1, NL-2700 MA Zoetermeer (NL).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): NIEUWENHUIZEN, Arie, Gijsbert [NL/NL]; Bolstraat 81, NL-3581 WV Utrecht (NL). VAN LAERE, Katrien, Maria, Jozefa [BE/NL]; Kamperfoeliestraat 11, NL-6666 WS Heteren (NL). RAGGERS, Rene, John [NL/NL]; Staalmeesterslaan 243, NL-1057 NX Amsterdam (NL).
- Published:  
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: COMBINATION OF FLAVONOID AND PROCYANIDIN FOR THE REDUCTION OF THE MAMMALIAN APPETITE

(57) Abstract: The present invention relates to a nutritional composition suitable for reducing appetite, a method for the treatment and/or prevention of overweight and a method for the reduction of a mammalian appetite. The weight reduction and/or appetite reduction is achieved by administration of procyanidin and a flavonoid selected from the group consisting of chrysin, flavone, precursors of these flavonoids that are convertible into the one of these flavonoids by gastrointestinal hydrolytic cleavage and mixtures thereof.

WO 2004/045604 A1

BEST AVAILABLE COPY

COMBINATION OF FLAVONOID AND PROCYANIDIN FOR THE REDUCTION OF THE MAMMALIAN APPETITE

- 5 The invention relates to a method for the prevention or treatment of overweight, the method comprising the administration of flavonoids and procyanidins.

BACKGROUND OF THE INVENTION

- 10 Overweight and obesity are major problems within the Western community. Due to increased consumption, decreased exercise and changes in the nutritional value of foodstuffs, many humans and companion animals are suffering from overweight or have difficulty maintaining a desirable weight. Many methods have been proposed to solve this problem, for example, via the administration of functional ingredients (e.g.  
15 nutritional supplements) which facilitate the reduction of overweight.

- In effect, overweight is caused by the ingestion of excess calories. Calories are for example ingested via high caloric meals. Within the art, several strategies are known for reducing caloric intake. These strategies include for example replacing the high  
20 caloric meals for low caloric meals (e.g. meal replacers); the ingestion of medicaments that reduce the absorption of high caloric components from the meal (e.g. lipase inhibitors); and the administration of appetite reducing agents.

- Currently, known appetite reducing agents have the disadvantage of causing severe side  
25 effects. Sibutramine is an appetite suppressant that is proposed to work via norepinephrine and serotonergic mechanisms in the brain. The drug has been described to have side effects, including high blood pressure, headache, dry mouth (which may increase the risk for dental disease), constipation and decreased sleep. Other reported side effects include: increased heart rate, dizziness, flushing, sweating, nausea.  
30 Presently, sibutramine is the only appetite suppressant that has been approved by the FDA for long-term use in a method for reducing overweight.

The present inventors have surprisingly found that chrysin (CAS Registry Number 480-40-0) as well as flavone (CAS Registry Number 525-82-6) are capable of reducing the appetite when administered orally, as described in the Applicant US co-pending application "METHOD FOR THE REDUCTION OF THE MAMMALIAN  
5 APPETITE" filed 18 November 2002 with US serial application number 10/295987 and incorporated herein by reference.

Typically, Chrysin (5,7-dihydroxyflavone) is a flavonoid that is advertised to promote muscle growth. Furthermore, chrysin has been described to possess anxiolytic  
10 properties (i.e. anxiety reducing properties) without exhibiting a sedative effect as given in US 5,756,538. Chrysin has also been described to treat any condition of elevated levels of unconjugated bilirubin in adults or children, such as Gilbert's syndrome or liver cirrhosis as given in WO 01/58410.

WO 99/22728 relates to compounds that inhibit 5 alpha -reductase. The compounds  
15 are used to treat prostate cancer, breast cancer, obesity, skin disorders and baldness. From Table 1 in the document it is apparent that chrysin is unsuitable as a compound to inhibit 5 alpha reductase, hence unsuitable to treat prostate cancer, breast cancer, obesity, skin disorder and baldness.

20 The present inventors have also found that procyanidins are capable of reducing the mammalian appetite when administered orally, as described in the Applicant co-pending application PCT/NL 02/00607 and incorporated herein by reference.

Procyanidins are known and used for their antioxidant properties. Still, these have also  
25 been described for their antiobesic properties, i.e. the intestinal lipase and carbohydrase reducing activity.

EP815857 describes an antiobestic agent comprising as the active ingredient tamarind seed coat extracts (procyanidin). According to this application, the tamarind seed coat extract or procyanidin can act as a carbohydrase inhibitor, blood sugar increase  
30 inhibitor, monosaccharide absorption inhibitor, cholic acid adsorptive excretion promoter, cholesterol lowering agent, blood triglyceride lowering agent and lipase inhibitor.

WO 00/54610 describes a food complement for dietetic and/or cosmetic purposes, containing anti-lipase properties, for oral administration. Said food complement is characterized in that it comprises a grape extract rich in or enriched with polyphenols.

- 5 The present inventors have now surprisingly found that a combination of flavone and/or chrysin combined with procyanidin is particularly suitable for reducing mammalian appetite, and can be suitably used in a method for the treatment of overweight. Reduction of appetite results in a reduced caloric intake.
- 10 Grape seed generally contains a minor percentage procyanidins. Further, combinations of chrysin and grape seed are known in the art, for example from Vitagrowth IV<sup>TM</sup>, a product advertised as an "Advanced Herbal Solution for Incontinency". However, such product only contains minor quantities of flavone, chrysin and procyanidin. Consequently, the product is deemed to comprise insufficient procyanidins and/or
- 15 chrysin to provide the appetite reducing effects when combined with chrysin.

## SUMMARY OF THE INVENTION

- 20 In one aspect of the present invention, there is provided a nutritional composition suitable for enteral administration comprising per dosage:
- a. between 5 mg and 10 grams of a flavonoid selected from the group consisting of chrysin, flavone, precursors of these flavonoids that are convertible into the one of these flavonoids by gastrointestinal hydrolytic cleavage and mixtures thereof; and
  - 25 b. between 10 mg and 12.5 g procyanidin.

In a further aspect the present invention relates a method for the treatment and/or prevention of overweight in a mammal, said method comprising administering to the mammal:

- 30 a. between 0.01 mg and 250 mg flavonoid per kg body weight of the mammal, said flavonoid being selected from the group consisting of chrysin, flavone, precursors

of these flavonoids that are convertible into the one of these flavonoids by gastrointestinal hydrolytic cleavage and mixtures thereof; and

b. between 0.1 and 100 mg procyanidin per kg body weight of the mammal.

5 In still a further aspect the present invention relates a method for the reduction of appetite in a mammal, said method comprising administering to the mammal:

a. between 0.01 mg and 250 mg flavonoid per kg body weight of the mammal, said flavonoid being selected from the group consisting of chrysin, flavone, precursors of these flavonoids that are convertible into the one of these flavonoids by

10 gastrointestinal hydrolytic cleavage and mixtures thereof; and

b. between 0.1 and 100 mg procyanidin per kg body weight of the mammal..

A further aspect of the present invention relates to the provision of an article of manufacture comprising a packaging with one or more of the above described dosages, in which said article bears a label indicating that the contents should be consumed by a human desiring to lose weight.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

20

### *Flavonoids*

The present inventors surprisingly found that chrysin and flavone are capable of reducing the mammalian appetite. Hence, the present method comprises the administration of an effective amount of a flavonoid selected from the group consisting of chrysin, flavone, precursors of these flavonoids that are convertible into the one of these flavonoids by gastrointestinal hydrolytic cleavage and mixtures thereof.

25 Preferably, the precursors of the flavonoids that are convertible into one of these flavonoids by gastrointestinal hydrolytic cleavage are selected from the group consisting of glycosides, rutinoides, glucuronoside, gentobioside and methyl ethers, more preferably glycosides.

30

For the purpose of the present invention, by the term "glycosides" it is meant glycosides of chrysin and/or glycosides of flavone.

Advantageously chrysin or a precursor thereof such as a glycoside thereof is used. Preferred glycosides of chrysin are selected from the group consisting of chrysin-5-O-glycoside and chrysin-7-O-glycoside. Most preferably chrysin is used.

5

The precursor of the flavonoids that are convertible into flavone or chrysin by gastrointestinal hydrolytic cleavage is preferably also converted into flavone or chrysin under (*in vitro*) conditions that simulate the gastrointestinal condition(s), preferably human gastrointestinal conditions. This typically involves incubating the precursor in a medium that simulate the human gastrointestinal conditions and observe if chrysin or flavone is formed. More preferably, the precursor is converted into chrysin or flavone under acidic conditions and/or by the action of one or more gastrointestinal enzymes, normally present in the gastrointestinal tract.

15

#### Dosage flavonoid

In order to achieve significant weight reduction and/or appetite reducing effect, it is desirable to administer at least 0.01 mg, preferably at least 0.1 mg, even more preferably at least 1 mg, most preferably at least 2 mg of the flavonoid per kg of body weight. Preferably the amount is administered on a daily basis, more preferably per serving. Preferably, the total amount of the present flavonoid does not exceed 250 mg per kg of body weight

A dosage, suitable for use in the present method, preferably contains at least 10 mg, more preferably at least 50 mg, even more preferably at least 100 mg, most preferably at least 200 mg of the flavonoid. To prevent undesirable side effects, the dosage preferably contains less than 10 g, more preferably less than 5 g, even more preferably less than 2.5 g of the flavonoid.

For a human adult, the present method preferably comprises the administration of a dosage containing between 10 mg and 10 grams, more preferably between 50 mg and 5 grams, even more preferably between 100 mg and 2.5 grams of the flavonoid

### Sources of the flavonoids

In a particularly preferred embodiment, the flavonoid, is provided by plant material containing the flavonoid, more preferably in the form of a plant isolate containing the flavonoid.

The term "plant isolate" as referred to herein, encompasses any fraction that can be obtained from a plant material by means of isolation techniques known in the art, e.g. extraction, distillation, squeezing etc. and that has an increased flavonoid content compared to the dry plant raw material. Preferably the plant material contains at least 1 wt.%, more preferably at least 5 wt.%, even more preferably at least at least 10 wt.%, most preferably at least 50 wt.% flavonoid based on the total dry weight of the plant material. Usually, the flavonoid content of the plant material does not exceed 99.5 wt.% based on the total dry weight of the plant raw material. Advantageously, synthetic chrysin is used.

15

According to a preferred embodiment the present flavonoid, preferably chrysin, is provided in the form of a plant material or extract from a plant selected from the group consisting of *Pinus aristata*, *Prunus domestica*, *Ulmus sieboldiana*, *Fluorensia resinosa*, *Oroxylum indicum*, *Scutellaria* spp., *Passiflora* spp. and mixtures thereof, more preferably in the form of a plant selected from the group consisting of *Pinus aristata*, *Prunus domestica*, species of *Passiflora* and mixtures thereof, most preferably selected from plant material or isolate from a plant selected from the group consisting of *Passiflora alata*, *Passiflora incarnata*, *Passiflora coerulea* and mixtures thereof.

20

### 25 Flavonoid content

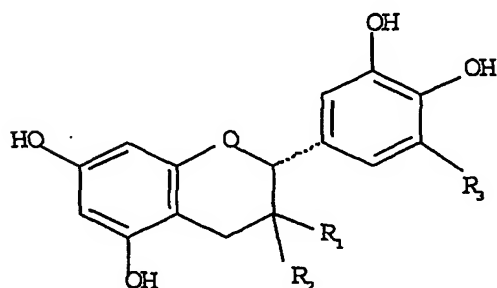
Advantageously, the present method comprises the administration of a serving or dosage containing at least 1 wt.%, more preferably at least 5 wt.%, even more preferably at least 10 wt.%, most preferably at least 25 wt.% of the present flavonoid based on the total dry weight of the dosage. Preferably the flavonoid content of the dosage does not exceed 90 wt.% flavonoid, more preferably does not exceed 50 wt.% based on the total dry weight of the dosage.

30

**Procyanidin**

Procyanidins have been known and used especially for their antioxidant properties and their carbohydrase inhibitory effect. It has surprisingly been found by the present  
 5 inventors that procyanidins have appetite reducing properties, when administered to a mammal in a therapeutically effective amount.

Procyanidins are members of the proanthocyanidins group. Proanthocyanidins involve procyanidin, prodelphinidin, propelargonidin, proguibourtinidin, profisetinidin, prorobinetinidin, proteracacidin, promelacacidin, proapigeninidin, proluteolinidin and  
 10 all of the stereoisomers thereof. The procyanidin used in the present invention is a polymer, comprising 2 or more units of one or more of the monomers as shown in the following formula:



15

**Figure 1: Structure of procyanidin monomer**

wherein:

- a.  $R_1 = \text{OH}$ ,  $R_2 = \text{H}$ ,  $R_3 = \text{H}$ ; or
- b.  $R_1 = \text{H}$ ,  $R_2 = \text{OH}$ ,  $R_3 = \text{H}$ ; or
- 20 c.  $R_1 = \text{gallic acid ester}$ ,  $R_2 = \text{H}$ ,  $R_3 = \text{H}$ ; or
- d.  $R_1 = \text{H}$ ,  $R_2 = \text{gallic acid ester}$ ,  $R_3 = \text{H}$

According to a preferred embodiment the procyanidin is mainly present as B-type  
 25 polymers, which have a single interflavanoid bond (in contrast to A-type procyanidin polymers, which have a second interflavanoid bond). Even more preferably at least 70 mol % of the procyanidin polymers are present as B-type polymers.

*Procyanidin: Source*

Procyanidins can be easily obtained from various sources. Preferably the procyanidins are obtained from a natural, more preferably a plant source. Preferably the procyanidins are obtained from a plant source selected from the group consisting of grape, pine, cocoa, tamarind, tomato, peanut, almond, apple, cranberry, blueberry and mixtures thereof, especially from the group consisting of pine bark, grape seed, tamarind seed husk, cocoa bean, apple peel, apple pericarp and mixtures thereof and most preferably from grape seed and/or pine bark. Advantageously, procyanidins from grape seed are used

*Procyanidins: Extract*

Typically procyanidins from plant sources comprise very low levels of procyanidins. Consequently, in order to accomplish the desired appetite reducing effect, vast amounts of the raw plant material would have to be consumed. The use of an extract of one of the procyanidin sources may avoid such discomfort. An additional advantage of the use of a more concentrated form of procyanidins, e.g. in the form of an extract, resides in the fact that procyanidins may be administered without co-administering a significant amount of caloric plant material. More importantly, however, the inventors believe that the use of compositions having an increased weight percentage of procyanidins provides an increased appetite reducing effect compared to procyanidin containing compositions having a lower weight percentage procyanidins.

Preferably, the procyanidin containing plant extract used in the current invention comprises at least 5 wt.%, more preferably at least 10 wt.%, even more preferably at least 25 wt.%, most preferably at least 50 wt.%, especially at least 75 wt.% procyanidin based on the dry weight of the extract. The term "extract" as used in the present invention refers to an isolate that has been obtained by means of solvent extraction.

*Procyanidin: Dosage*

In accordance with a preferred embodiment, a dosage comprising between 0.1 and 100 mg procyanidin per kg body weight should be administered to a mammal. More preferably the method comprises the administration of between 0.5 and 75 mg, even more preferably between 0.75 and 50 mg, most preferably between 1 and 20 mg,

especially between 2 mg and 10 mg procyanidin per kg body weight.

For human subjects above the age of about 10 years, the present dosage contains between 10 mg and 12.5 g, preferably between 25 mg and 10 g, more preferably between 50 mg and 5 gram, more preferably between 100 mg and 3 gram, most  
5 preferably between about 200 mg and 2 gram, especially between 250 mg and 1 gram procyanidin.

According to a preferred embodiment, the appetite reducing composition comprising procyanidin, comprises at least 1 wt.% procyanidin based on dry weight, more  
10 preferably at least 2 wt.%, even more preferably at least 5 wt.%, most preferably at least 8 wt.%, especially at least 12.5 wt.%. Preferably the procyanidin content of the dosage does not exceed 90 wt.% procyanidin, more preferably does not exceed 50 wt.% based on dry weight.

#### 15 Nutritional composition

*In a further aspect, the present invention provides a nutritional composition for enteral administration comprising per serving: a) between 5 mg and 10 grams of a flavonoid selected from the group consisting of chrysin, flavone, precursors of these flavonoids that are convertible into the one of these flavonoids by gastrointestinal hydrolytic  
20 cleavage and mixtures thereof; and b) between 10 mg and 12.5 g procyanidin.*

Preferably the present nutritional composition is in the form of a unit dosage. Whenever the term dose or dosage is used within this disclosure, any dosage form is encompassed which can be administered, preferably orally, within a fairly narrow time  
25 span. Whenever reference is made to a certain quantity that is administered per dose or dosage, said quantity is preferably administered within one hour, more preferably within 15 minutes, even more preferably within 5 minutes.

#### *Flavonoid and procyanidin: Synergism*

30 It is the inventors belief that the procyanidin combined with one or more of the present flavonoids synergistically reduce the appetite of a mammal. The effect is deemed to be

synergistically increased if sufficient amounts of the flavonoid, preferably chrysin, and procyanidins are administered simultaneously.

5 Treatment and prevention of overweight

The present invention provides a method for reducing or preventing overweight or obesity, and a method for the reduction the appetite in a mammal. The term overweight as used in the present invention refers to a bodyweight that is above the desired bodyweight. The present method is particularly suitable for humans, especially most  
10 advantageous for human subjects who have a body mass index above 25.

The present invention also provides an article of manufacture comprising packaged unit dosages according to the present invention, in which said article bears a label indicating the contents should be consumed by a human desiring to lose weight. Hence, packaged  
15 nutritional supplements and dietary products, which have been provided with labels that explicitly or implicitly direct the consumer towards the use of said supplement or product in accordance with one or more of the above or below purposes, are encompassed by the present invention. Such labels may for example make reference to the method for the treatment of overweight by incorporation of terminology like "slim",  
20 "lean", "weight reduction", "appetite reduction", "satiety" and the like. The overweight reducing properties of the product may be indicated via indicia such as pictures, drawings and other indicia from which a consumer can conclude that the product aims to treat or prevent overweight.

25 The present invention preferably does not relate to the use of chrysin for counteracting side effects of the androgens, anabolic steroids or prohormones. Androgens, anabolic steroids and prohormones are often used to increase muscle mass, and thus body weight. In a preferred embodiment the present method does not comprise the administration of a member selected from the group consisting of an androgens,  
30 anabolic steroids and prohormones, i.e. comprises the administration of a dosage free of androgens, anabolic steroids and prohormones. In other words, the present method preferably does not comprise the administration of any androgens, anabolic steroids or prohormones. The term "prohormones" as used in the present invention relates to

metabolic precursors which raise the level of the male hormones testosterone and/or 19-nortestosterone *in vivo*, preferably to those ingredients that are metabolic precursors of hormones.

## 5 Thermogenic ingredient

Due to the appetite reducing effects of the present combination of flavonoid and procyanidin, the *in vivo* nutrient availability becomes limited. After some time, this may translate into a hunger feeling. Thermogenic ingredients are capable of increasing the *in vivo* availability of free fatty acids from *in vivo* stored fat (e.g. triglycerides stored in adipose tissue. Co-administration of the thermogenic ingredient together with the present combination of flavonoid and procyanidin is believed to prolong the appetite reducing effects of the flavonoid and procyanidin. Additionally, in a method for treating overweight and reducing adiposity it is especially advantageous to preferentially oxidate fatty acids, as it reduces fat stores. Hence, the flavonoid, procyanidin and thermogenic ingredient are deemed to synergistically reduce overweight.

Preferably the thermogenic ingredient is selected from the group consisting of caffeine, synephrine, ephedrine, Bacopa plant material, *Paullinia cupana* and *Ilex paraguariensis*, more preferably is *Ilex paraguariensis*.

The thermogenic ingredient is preferably administered in a daily amount of between 0.1 mg and 25 mg per kg of body weight. According to a particularly preferred embodiment the thermogenic ingredient is administered in a daily amount between 0.5 and 15 mg, more preferably between 1 and 10 mg thermogenic ingredient per kg body weight.

The dosage according to the present invention preferably comprises between 5 and 4000 mg thermogenic ingredient. More preferably, a dosage comprises between 25 and 2000 mg, even more preferably between 50 and 1000 mg, most preferably between 100 and 500 mg thermogenic ingredient.

Advantageously, the present method comprises the co-administration of caffeine. The caffeine used in the present invention may be naturally, semi-synthetically or synthetically derived. According to a preferred embodiment naturally derived caffeine

is used. Preferred sources of naturally derived caffeine include herbal extracts comprising between 5 and 95 % caffeine based on the dry weight of the herbal extract, more preferably between 10 and 50 %. A preferred source of natural caffeine is a plant material selected from the group consisting of *Paullinia cupana* and *Ilex paraguariensis*. Most preferably *Ilex paraguariensis* is used.

The caffeine is preferably administered in a daily amount of between 0.1 mg and 25 mg per kg of body weight. According to a particularly preferred embodiment the caffeine is administered in a daily amount between 0.5 and 15 mg, more preferably between 1 and 10 mg caffeine per kg body weight.

The dosage according to the present invention preferably comprises between 5 and 4000 mg caffeine. More preferably, a dosage comprises between 25 and 2000 mg, even more preferably between 50 and 1000 mg, most preferably between 100 and 500 mg caffeine.

#### Fibers

In a preferred embodiment, the present invention comprises the coadministration of fibers. The fibers further increase the satiation, by providing a feeling of fullness which is probably caused by the a reduced rate of stomach emptying.

The fiber used in accordance with the present invention is preferably selected from the group consisting of gum arabic, sodium carboxymethylcellulose, methylcellulose, guar gum, gellan gum, locust bean gum, konjac flour, hydroxypropyl methylcellulose, tragacanth gum, karaya gum, gum acacia, chitosan, arabinoglactins, glucomannan, xanthan gum, alginate, pectin,  $\beta$ -glucans, carrageenan and psyllium, more preferably from the group consisting of glucomannan, guar gum, gellan gum and locust bean gum.

The fiber is preferably administered in a daily amount of between 0.5 mg and 100 mg per kg of body weight. According to a particularly preferred embodiment the fiber is administered in a daily amount between 2 and 75 mg, more preferably between 2.5 and 50 mg fiber per kg body weight.

The dosage according to the present invention preferably comprises between 5 mg and 15 grams fiber. More preferably, a dosage comprises between 50 mg and 10 grams, even more preferably between 100 mg and 5000 mg, most preferably between 250 mg and 2500 mg fiber.

5

*Reduction of appetite*

The present invention is especially aimed at the reduction or prevention of appetite and/or feelings of hunger. The method according to the invention can, for example, be used in a method for inducing satiety, inducing satiation, satisfying hunger or reducing

10

craving urges. Generally, an individual's feelings and sensations between the start of a first meal and the next meal go through different phases. A set of sensations is usually discriminated within the art. If satiety is evaluated, several phases can be used to express the satiety after a meal. These can be termed very full, full, appetite and hungry. Preferably the present invention combination of the flavonoid and procyanidin is administered in the

15

phases appetite, hunger or at the end of the full phase, more preferably in the appetite or hunger phase. Preferably, the flavonoid and procyanidin is administered about 1-8 hours, more preferably about 2-6 hours after consumption of a meal. Typically the procyanidin and flavonoid is administered between 1 hour after one meal and 1 hour prior to the next meal. In a further aspect, the procyanidin and flavonoid can be taken shortly before the meal or even during a meal, for example when the meal is expected to provide insufficient satisfaction. This may occur when the individual is subjected to a weight loss program. Hence, the nutritional composition can be advantageously used in a method for the reduction of the adverse side effects experienced during a weight loss program, i.e. administered to subjects participating in a weight loss program.

20

25

Additionally, appetite reducing agents are useful in several other applications. The present invention combination of flavonoid and procyanidin can for example be used to provide comfort to subjects having limited access to foodstuffs, such as for example military personnel during a long mission.

30

*Administration*

According to a preferred embodiment the present method comprises the enteral, more preferably the oral administration of the flavonoid and procyanidin. Particularly suitable is the administration of a dosage or serving containing both the flavonoid and the procyanidin.

The dosage used in the present method can be applied in any suitable form, such as bars, pills, capsules, gels, liquid, etc. However, it is preferably provided in the form of a pill, tablet or capsule. Preferably a dosage does not consist of more than 3 tablets, capsules or pills, even more preferably consists of a single pill, capsule or tablet.

Advantageously, at least two dosages, more preferably at least three dosages, are administered in one day. In the present method a daily dosage of the preparation as used in the present invention can include one or more pills, tablets or capsules. Preferably a daily dosage consists of 1 to 6 pills, tablets or capsules.

A dosage is preferably in a solid or semisolid form, more preferably in a form selected from the group consisting of pills, capsules, tablets, caplet, microparticles and microspheres. The solid or semisolid dosage form preferably has a weight between 0.1 and 30 grams, more preferably between 0.2 and 10 grams.

For easy administration, the dosage preferably contains a pharmaceutically acceptable carrier. These carriers may be selected from sugars, starches, cellulose and its derivatives, malt, gelatine, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffered solutions, emulsifiers, isotonic saline, and pyrogen-free water

The dosage preferably has a caloric value below 100 kcal, more preferably below 50 kcal even more preferably below 10 kcal. A dosage preferably has a weight between 0.2 and 4 grams, even more preferably between 0.5 and 3 grams.

The following are non-limiting examples illustrating the present invention:

EXAMPLES

Example 1: Weight loss supplement for humans

Soft gelatin capsule containing,  
800 mg Vitis vinifera extract (comprising 85 wt.% procyanidins); and  
200 mg chrysin (min 99%, Pharm Chemical, Shanghai, China)

5 Example 2: Appetite reducing supplement for humans

Soft gelatin capsule containing,  
400 mg pycnogenol (comprising 65 wt.% procyanidins);  
800 mg chrysin (min 99%, Pharm Chemical, Shanghai, China); and  
200 mg excipient

10

Example 3: Anti-Craving supplement for humans

A beverage containing per 200 ml serving  
800 mg Vitis vinifera extract (comprising 85 wt.% procyanidins)  
250 mg Gymema sylvestre extract (comprising 25 wt.% gymnemic acid); and  
15 200 mg chrysin (min 99%, Pharm Chemical, Shanghai, China)

Example 4: Appetite reducing bar for children

Cereal bar containing:  
50 mg procyanidins in the form of apple chunks;  
20 30 gram oat bran;  
50 mg chrysin (min 99%, Pharm Chemical, Shanghai, China); and  
200 mg guar gum

Example 5: Appetite reducing supplement for humans

25 Soft gelatin capsule containing,  
200 mg Vitis vinifera extract (comprising 25 wt.% procyanidins);  
200 mg chrysin (min 99%, Pharm Chemical, Shanghai, China); and  
100 mg caffeine

30

CLAIMS:

1. A preparation containing a combination of flavonoid and procyanidin capable of  
5 reducing appetite for use in method for the treatment and/or prevention of  
overweight in a mammal, said method comprising administering to the mammal:
  - a. a. between 0.01 mg and 250 mg flavonoid per kg body weight of the mammal,  
said flavonoid being selected from the group consisting of chrysin, flavone,  
precursors of these flavonoids that are convertible into the one of these  
10 flavonoids by gastrointestinal hydrolytic cleavage and mixtures thereof; and
  - b. between 0.1 and 100 mg procyanidin per kg body weight of the mammal.
2. A preparation containing a combination of flavonoid and procyanidin capable of  
15 reducing appetite for use in a method for the reduction of appetite in a mammal,  
said method comprising administering to the mammal:
  - a. a. between 0.01 mg and 250 mg flavonoid per kg body weight of the mammal,  
said flavonoid being selected from the group consisting of chrysin, flavone,  
precursors of these flavonoids that are convertible into the one of these  
20 flavonoids by gastrointestinal hydrolytic cleavage and mixtures thereof; and
  - b. between 0.1 and 100 mg procyanidin per kg body weight of the mammal..
3. The preparation according to claim 1 or 2, wherein the flavonoid is chrysin.
- 25 4. The preparation according to any one of the preceding claims, wherein the method  
comprises the administration of a dosage containing a combination of the flavonoid  
and procyanidin.
5. The preparation according to claim 4, wherein the dosage contains at least 1 wt.%  
30 of the flavonoid based on the total dry weight of the dosage.
6. The preparation according to claim 4, wherein the dosage contains at least 1 wt.%  
of procyanidin based on the total dry weight of the dosage.

7. The preparation according to any one of the preceding claims, wherein the flavonoid and procyanidin are administered orally.
- 5 8. The preparation according to any one of the preceding claims, further comprising a thermogenic ingredient.
9. The preparation according claim 8, wherein the thermogenic ingredient is caffeine.
- 10 10. The preparation according to any one of the preceding claims, further comprising between 0.5 mg and 100 mg fiber per kg of body weight of the mammal.
11. A nutritional composition suitable for enteral administration comprising per dosage:
  - a. between 5 mg and 10 grams of a flavonoid selected from the group consisting of  
15 chrysin, flavone, precursors of these flavonoids that are convertible into the one of these flavonoids by gastrointestinal hydrolytic cleavage and mixtures thereof;  
and
  - b. between 10 mg and 12.5 g procyanidin.
- 20 12. The nutritional composition according to claim 11, wherein the flavonoid component is chrysin.
13. The nutritional composition according to claims 11 or 12, further comprising a thermogenic ingredient.
- 25 14. The nutritional composition according to claim 13, wherein the thermogenic ingredient is caffeine.
15. Article of manufacture comprising a packaging with one or more of the dosages  
30 according to any one of claims 11-14, in which said article bears a label indicating the contents should be consumed by a human desiring to lose weight.

# INTERNATIONAL SEARCH REPORT

International No  
PCT/NL 03/00198

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/352 A61K31/522 A61K35/00 A23L1/29 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, BIOSIS, WPI Data, EMBASE, FSTA

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 815 857 A (SUNTORY LTD) 7 January 1998 (1998-01-07) cited in the application page 2, line 5,6 page 3, line 32-40 page 4, line 5,6,41-50 page 5, line 1-30,40-43,49,52,53 page 6, line 1-23,38-43	1-7, 11, 12, 15
Y	EP 0 829 261 B (DIRECTOR GENERAL OF SHIKOKU NA) 18 March 1998 (1998-03-18) page 2, line 1,2,27-36 claims 1-4	1-7, 11, 12, 15
	---	
	--- --	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

7 July 2003

Date of mailing of the international search report

31/07/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3018

Authorized officer

Houyvet, C

# INTERNATIONAL SEARCH REPORT

Internat application No  
PCT/NL 03/00198

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 01 74345 A (INGRAM JONATHAN) 11 October 2001 (2001-10-11) page 1, paragraph 2 page 3, paragraphs 2,3 page 4, paragraphs 1,4,5 page 5, paragraphs 1,2,4 page 7, paragraph 4 -page 8, paragraph 1 page 9, paragraphs 2,3</p>	1-7,11, 12,15
Y	<p>WO 99 22728 A (ARCH DEV CORP ;LIAO SHUTSUNG (US); HIIPAKKA RICHARD A (US)) 14 May 1999 (1999-05-14) cited in the application page 1, line 11-15 page 12, line 3-10 claims 1,6; figure 1</p>	1-7,11, 12,15
Y	<p>FR 2 790 645 A (ARKOPHARMA LAB) 15 September 2000 (2000-09-15) page 1, line 1-11 page 2, line 15 -page 3, line 3 page 6, line 15-26</p>	1-7,11, 12,15
Y	<p>PATENT ABSTRACTS OF JAPAN vol. 1998, no. 01, 30 January 1998 (1998-01-30) &amp; JP 09 227398 A (ZERIA PHARMACEUT CO LTD), 2 September 1997 (1997-09-02) abstract</p>	1-7,11, 12,15
Y	<p>US 2001/051160 A1 (JACOBS ROBERT H) 13 December 2001 (2001-12-13) page 1, paragraph 5 page 2, paragraphs 13,20,24,25 page 3, paragraphs 26-28</p>	8-10,13, 14
Y	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; December 1997 (1997-12) DOUCET E ET AL: "Food intake, energy balance and body weight control." Database accession no. PREV199800081806 XP002246534 abstract &amp; EUROPEAN JOURNAL OF CLINICAL NUTRITION, vol. 51, no. 12, December 1997 (1997-12), pages 846-855, ISSN: 0954-3007</p>	8-10,13, 14

# INTERNATIONAL SEARCH REPORT

Internal application No  
PCT/NL 03/00198

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0815857	A	07-01-1998	EP 0815857 A1 US 6294190 B1 WO 9723210 A1 JP 9291039 A	07-01-1998 25-09-2001 03-07-1997 11-11-1997
EP 0829261	B	18-03-1998	JP 2829387 B2 JP 10087486 A DE 69621801 D1 DE 69621801 T2 EP 0829261 A2 US 5776906 A	25-11-1998 07-04-1998 18-07-2002 23-01-2003 18-03-1998 07-07-1998
WO 0174345	A	11-10-2001	AU 5307001 A WO 0174345 A2 US 2002010141 A1	15-10-2001 11-10-2001 24-01-2002
WO 9922728	A	14-05-1999	AU 1289899 A EP 1027045 A1 WO 9922728 A1 US 2003105030 A1 US 6576660 B1	24-05-1999 16-08-2000 14-05-1999 05-06-2003 10-06-2003
FR 2790645	A	15-09-2000	FR 2790645 A1 AU 3169500 A BR 0008926 A CA 2364046 A1 CN 1343100 T EP 1161157 A1 WO 0054610 A1 JP 2002538802 T NZ 514024 A ZA 200107441 A	15-09-2000 04-10-2000 18-12-2001 21-09-2000 03-04-2002 12-12-2001 21-09-2000 19-11-2002 28-09-2001 16-05-2002
JP 09227398	A	02-09-1997	NONE	
US 2001051160	A1	13-12-2001	US 2001041675 A1	15-11-2001

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☒ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☒ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**